

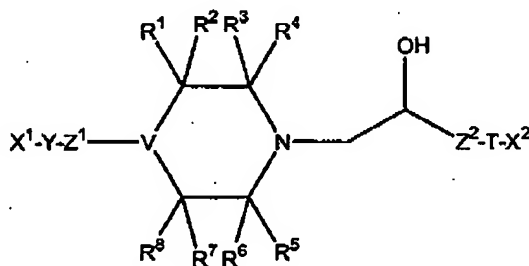
Response to July 6, 2005, Office Action  
 Atty Dkt No. 03-0185  
 Application No. 10/759,555

# APPENDIX A

## CLEAN COPY OF CLAIMS AS AMENDED HEREIN

1. A compound of Formula I:

wherein:



Formula I

$R^1, R^2, R^3, R^4, R^5, R^6, R^7,$  and  $R^8$  are hydrogen, lower alkyl, or  $-C(O)R$ ;

in which R is  $-OR^9$  or  $-NR^9R^{10}$ , where  $R^9$  and  $R^{10}$  are hydrogen or lower alkyl; or

$R^1$  and  $R^2, R^3$  and  $R^4, R^5$  and  $R^6, R^7$  and  $R^8$ , when taken together with the carbon to which they are attached, represent carbonyl; or

$R^1$  and  $R^5$ , or  $R^1$  and  $R^7$ , or  $R^3$  and  $R^5$ , or  $R^3$  and  $R^7$ , when taken together form a bridging group  $-(CR^{12}R^{13})_n$ , in which n is 1, 2 or 3, and  $R^{12}$  and  $R^{13}$  are independently hydrogen or lower alkyl;

with the proviso that

- (a) the maximum number of carbonyl groups is 1;
- (b) the maximum number of  $-C(O)NR^9R^{10}$  groups is 1; and
- (c) the maximum number of bridging groups is 1;

T is oxygen, sulfur, or  $NR^{11}$ , in which  $R^{11}$  is hydrogen or lower alkyl;

V is  $-N<$ ;

$X^1$  is hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

$X^2$  is optionally substituted aryl or optionally substituted heteroaryl;

Y is optionally substituted dihydroheteroaryl; and

Response to July 6, 2005, Office Action  
Atty Dkt No. 03-0185  
Application No. 10/759,555

Z<sup>1</sup> and Z<sup>2</sup> are independently optionally substituted alkylene of 1-4 carbon atoms.

2. A compound of claim 1, wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, and R<sup>8</sup> are independently chosen from hydrogen and methyl
3. A compound of claim 2, wherein X<sup>1</sup> is optionally substituted aryl and X<sup>2</sup> is optionally substituted heteroaryl.
4. The compound of claim 3, wherein Z<sup>1</sup> is methylene and Z<sup>2</sup> is methylene or ethylene.
5. The compound of claim 4, wherein Y is optionally substituted dihydroheteroaryl in which the hetero atoms are chosen from nitrogen and oxygen.
6. The compound of claim 5, wherein T is oxygen, X<sup>1</sup> is optionally substituted phenyl, and Y is optionally substituted isoxazolyl.
7. The compound of claim 6, wherein X<sup>2</sup> is optionally substituted benzothiazolyl.
8. The compound of claim 7, wherein Y is optionally substituted 5-(4,5-dihydroisoxazol-3-yl).
9. The compound of claim 8, wherein X<sup>1</sup> is 4-(trifluoromethyl)phenyl, X<sup>2</sup> is 2-methylbenzothiazol-5-yl, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, and R<sup>8</sup> are hydrogen, and Z<sup>2</sup> is methylene, namely 1-(2-methylbenzothiazol-5-yloxy)-3-[4-({5-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]propan-2-ol.
10. The compound of claim 9, namely (2R)-1-(2-methylbenzothiazol-5-yloxy)-3-[4-({5-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]propan-2-ol.

Response to July 6, 2005, Office Action  
Atty Dkt No. 03-0185  
Application No. 10/759,555

11. The compound of claim 8, wherein  $X^1$  is 2-(trifluoromethyl)phenyl,  $X^2$  is 2-methylbenzothiazol-5-yl,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ , and  $R^8$  are hydrogen, and  $Z^2$  is methylene, namely 3-(2-methylbenzothiazol-5-yloxy)-1-[4-({5-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]propan-2-ol.

12. The compound of claim 11, namely (2R)-3-(2-methylbenzothiazol-5-yloxy)-1-[4-({5-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]propan-2-ol.

13. The compound of claim 8, wherein  $X^1$  is 4-(trifluoromethyl)phenyl,  $X^2$  is 2-methylbenzothiazol-5-yl,  $R^1$ ,  $R^2$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ , and  $R^8$  are hydrogen,  $R^3$  is (S)-methyl, and  $Z^2$  is methylene, namely 1-[(2S)-2-methyl-4-({5-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

14. The compound of claim 13, namely (2R)-1-[(2S)-2-methyl-4-({5-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

15. The compound of claim 8, wherein  $X^1$  is 2-(trifluoromethyl)phenyl,  $X^2$  is 2-methylbenzothiazol-5-yl,  $R^1$ ,  $R^3$ ,  $R^2$ ,  $R^4$ ,  $R^5$ ,  $R^6$ , and  $R^8$  are hydrogen,  $R^7$  is (S)-methyl, and  $Z^2$  is methylene, namely 1-[(3S)-3-methyl-4-({5-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

16. The compound of claim 15, namely (2R)-1-[(3S)-3-methyl-4-({5-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

Response to July 6, 2005, Office Action  
Atty Dkt No. 03-0185  
Application No. 10/759,555

17. The compound of claim 8, wherein  $X^1$  is 4-(trifluoromethyl)phenyl,  $X^2$  is 2-methylbenzothiazol-5-yl,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ , and  $R^8$  are hydrogen,  $R^7$  is (S)-methyl, and  $Z^2$  is methylene, namely 3-[(3S)-3-methyl-4-({5-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

18. The compound of claim 17, namely (2R)-3-[(3S)-3-methyl-4-({5-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

19. The compound of claim 8, wherein  $X^1$  is 2-(trifluoromethyl)phenyl,  $X^2$  is 2-methylbenzothiazol-5-yl,  $R^1$ ,  $R^2$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ , and  $R^8$  are hydrogen,  $R^3$  is (S)-methyl, and  $Z^2$  is methylene, namely 1-[(2S)-2-methyl-4-({5-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

20. The compound of claim 19, namely (2R)-1-[(2S)-2-methyl-4-({5-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

21. The compound of claim 7, wherein Y is optionally substituted 3-(4,5-dihydroisoxazol-5-yl).

22. The compound of claim 21, wherein  $X^1$  is 4-(trifluoromethyl)phenyl,  $X^2$  is 2-methylbenzothiazol-5-yl,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ , and  $R^8$  are hydrogen, and  $Z^2$  is methylene, namely 1-[4-({3-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-5-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

23. The compound of claim 22, namely (2R)-1-[4-({(5R)-3-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-5-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

Response to July 6, 2005, Office Action  
Atty Dkt No. 03-0185  
Application No. 10/759,553

24. The compound of claim 21, wherein  $X^1$  is 2-(trifluoromethyl)phenyl,  $X^2$  is 2-methylbenzothiazol-5-yl,  $R^1, R^2, R^3, R^4, R^5, R^6, R^7$ , and  $R^8$  are hydrogen, and  $Z^2$  is methylene, namely 1-[4-({3-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-5-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

25. The compound of claim 24, namely (2R)-1-[4-({(5R)-3-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-5-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

26. The compound of claim 21, wherein  $X^1$  is 4-fluorophenyl,  $X^2$  is 2-methylbenzothiazol-5-yl,  $R^1, R^2, R^4, R^5, R^6, R^7$ , and  $R^8$  are hydrogen,  $R^3$  is (S)-methyl, and  $Z^2$  is methylene, namely 1-(4-{{(5R)-3-(4-fluorophenyl)(4,5-dihydroisoxazol-5-yl)}methyl}(2S)-3-methylpiperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

27. The compound of claim 26, namely (2R)-1-(4-{{(5R)-3-(4-fluorophenyl)(4,5-dihydroisoxazol-5-yl)}methyl}(2S)-3-methylpiperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

28. The compound of claim 21, wherein  $X^1$  is phenyl,  $X^2$  is 2-methylbenzothiazol-5-yl,  $R^1, R^2, R^4, R^5, R^6, R^7$ , and  $R^8$  are hydrogen,  $R^3$  is (S)-methyl, and  $Z^2$  is methylene, namely 1-{4-[[{(5R)-3-phenyl(4,5-dihydroisoxazol-5-yl)}methyl](2S)-2-methylpiperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

29. The compound of claim 28, namely (2R)-1-{4-[[{(5R)-3-phenyl(4,5-dihydroisoxazol-5-yl)}methyl](2S)-2-methylpiperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

30. A method of treating a disease state chosen from diabetes, damage to skeletal muscles resulting from trauma or shock and a cardiovascular disease in a mammal by administration of a therapeutically effective dose of a compound of claim 1.

Response to July 6, 2005, Office Action  
Attr Dkt No. 03-0185  
Application No. 10/759,555

31. The method of claim 30, wherein the cardiovascular disease is atrial arrhythmia, intermittent claudication, ventricular arrhythmia, Prinzmetal's (variant) angina, stable angina, unstable angina, congestive heart disease, or myocardial infarction.

32. The method of claim 30, wherein the disease state is diabetes.

33. A pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and a therapeutically effective amount of a compound of claim 1.